

Primary lymphedema (clinical classification).

Diagnosis	Frequency ^{22,31,32,33} (% of all primary forms)
Congenital (onset <2 years after birth)	6-12
Familial, autosomal dominant (Nonne-Milroy disease)	
Familial, non-dominant inheritance	
Sporadic (most common congenital form)	
Lymphedema precox (onset between 2-35 years)	77-94
Familial, autosomal recessive (Meige disease)	
Sporadic (83-94% of all lymphedema precox)	
Lymphedema tarda (onset after 35 years of age)	11

Figure 1A

Functional Classification of Primary Lymphedema

	Distal Obliteration (80%)	Proximal Obliteration (10%)	Hyperplasia* (10%)
Gender	Female	Male or female	Male or female
Onset	Puberty	Any age	Congenital
Time		Whole leg, thigh; unilateral	Whole leg; unilateral or bilateral
Location	Ankle; bilateral		
Progression	Slow	Rapid	Progressive
Family history	Frequently positive	None	Frequently positive

Adapted from Browse NL: The diagnosis and management of primary lymphedema. J Vasc Surg 3:181, 1986.
*With or without reflux of chyle.

Figure 1B

Secondary lymphedema.

Blockade at the level of the lymph node
Regional lymph node dissection
Axillary (post-mastectomy lymphedema)
Pelvic and para-aortic (leg and groin lymphedema)
Neck (head and neck lymphedema)
Neoplastic disease
Hodgkin lymphoma
Metastatic cancer
Prostate cancer
Cervical cancer
Breast cancer
Melanoma
Disruption or obliteration of lymphatic channels
Surgery, e.g. ilio-femoral bypass
Direct injury, e.g. trauma of the medial aspect of the thigh
Radiation-induced fibrosis
Neoplastic infiltration of lymphatic channels
Rheumatoid arthritis
Filariasis
Recurrent infection, e.g. erysipelas

Figure 1C

Lymphangiographic Patterns Normal vs. Primary Lymphedema

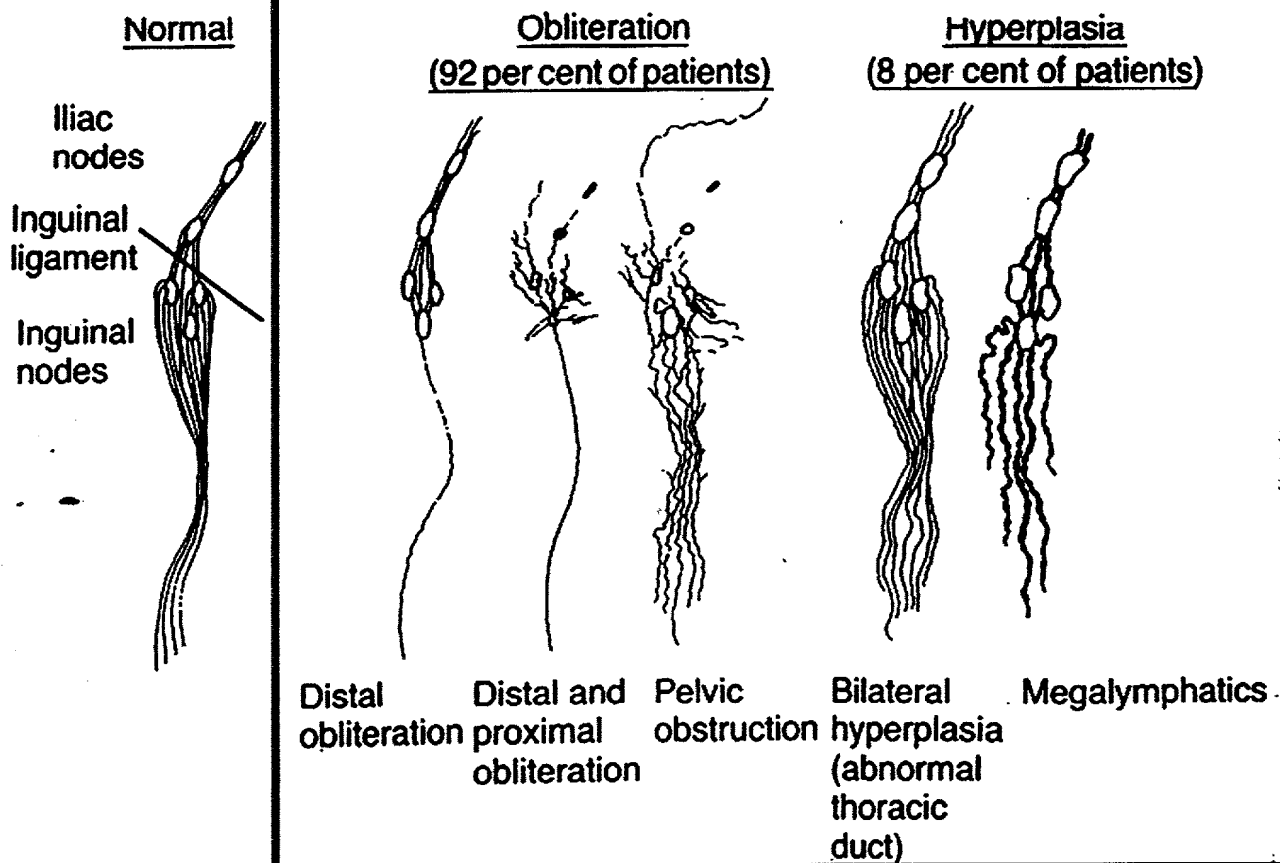


Figure 2

Rabbit Ear Lymphedema Model

Clinical Appearance - 5Month



Control

VEGF-2

Figure 3

Rabbit Ear Lymphedema Model Lymphoscintigraphy - 5 Month Post-Op

VEGF-2

*CONTROL

Figure 4

Rabbit Ear Lymphedema Model
Lymphoscintigraphy-Orientation

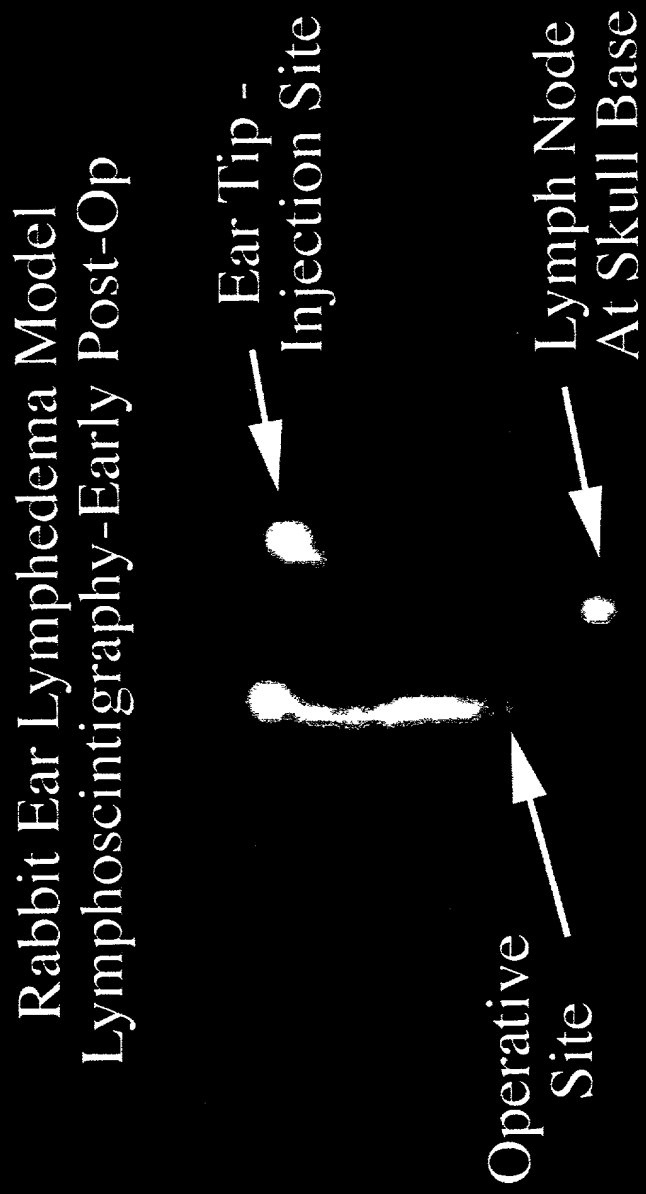


Figure 6

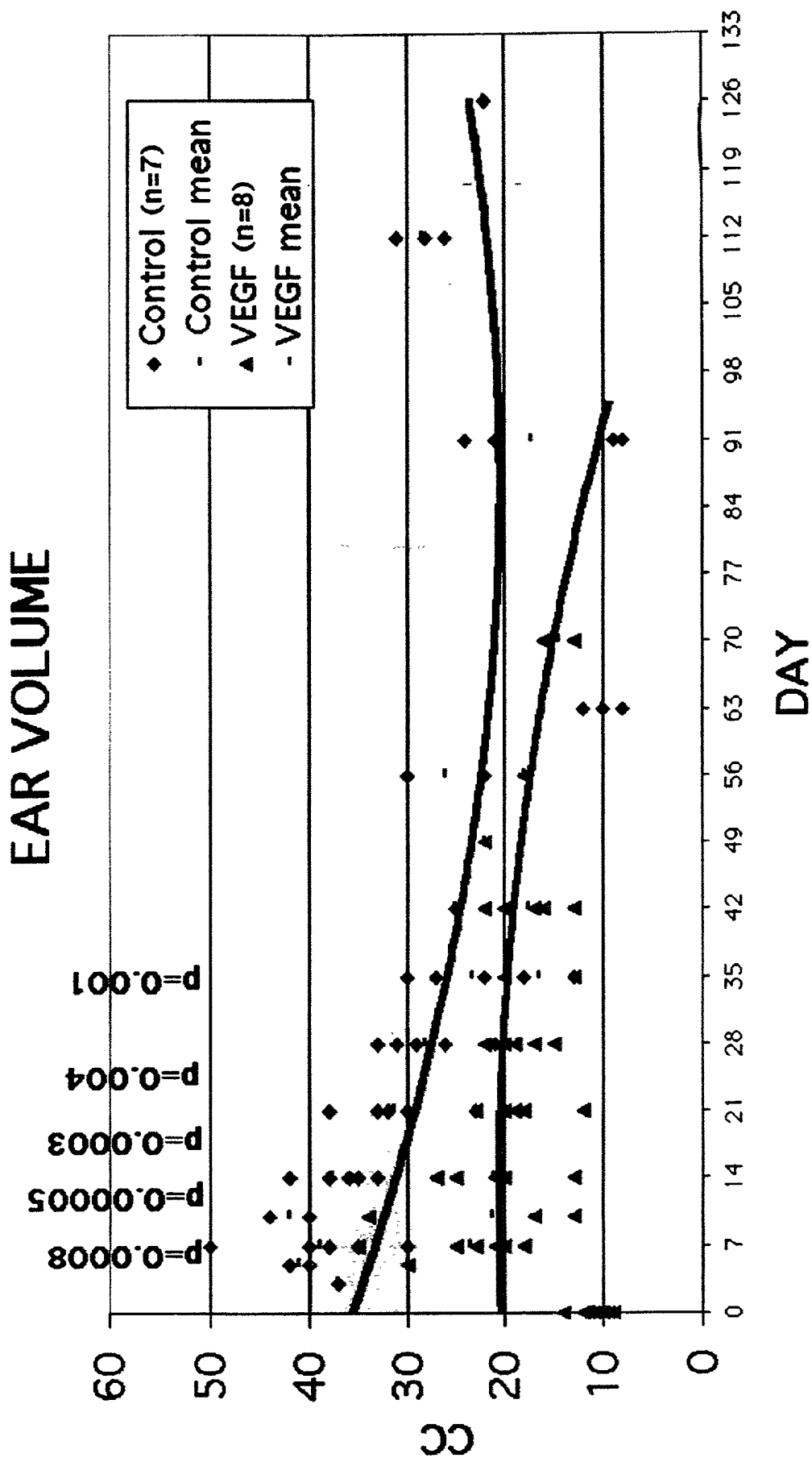


Figure 7

Rabbit Ear Lymphedema Model 3 Days Post-Op

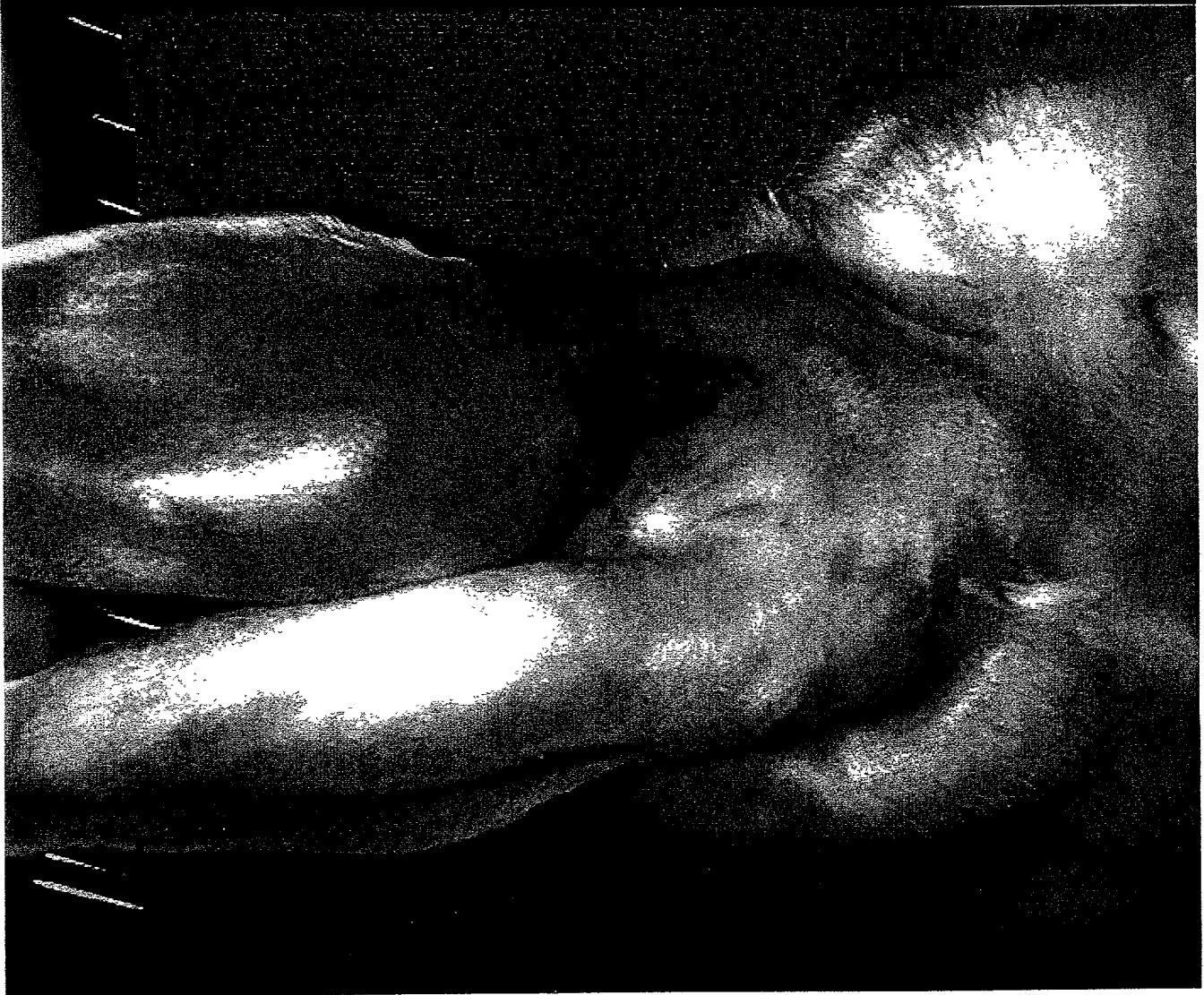


Figure 8

Human Lymphoscintigraphy Right Lower Extremity

Pre-VEGF2

Post-VEGF2

Thigh

Knee

Foot

Figure 9

**Ultrasound Imaging of Intra-Muscular
VEGF-2 Gene Transfer: Lymphedema**

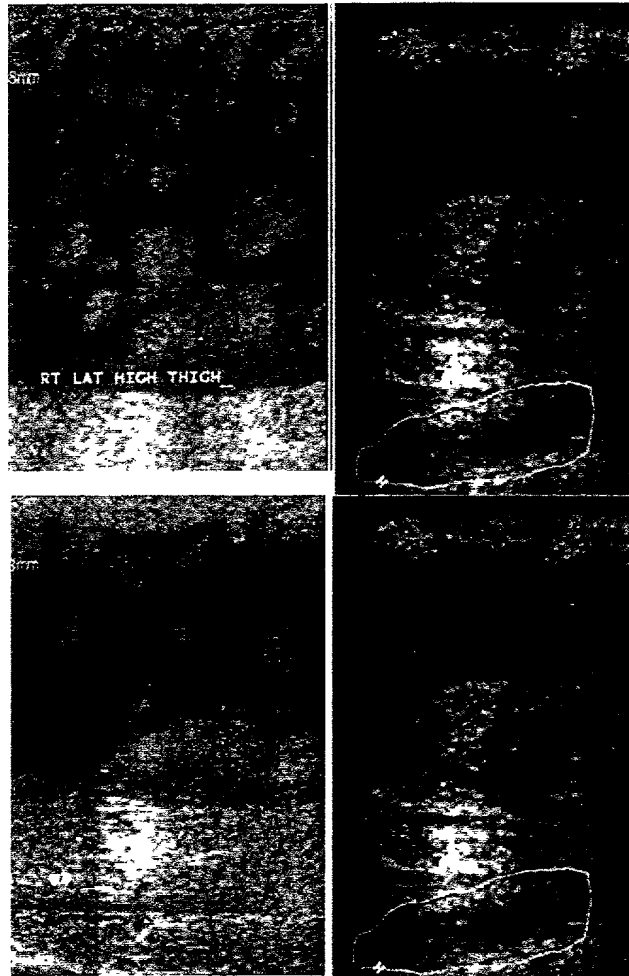
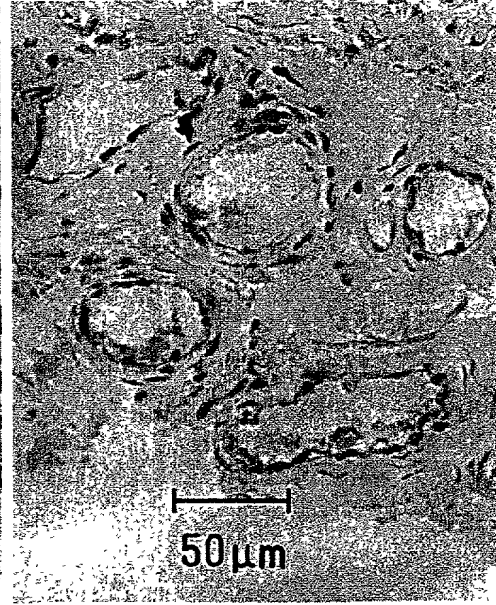
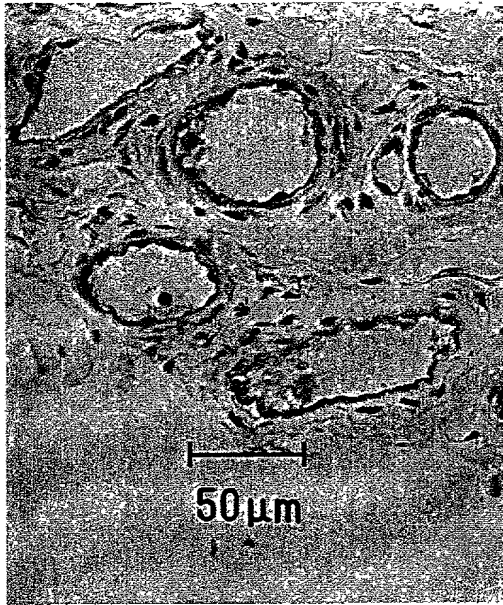


Figure 10

FLT-4 positive Ab

FLT-4 negative Ab
(MOPC positive Ab)

Patient



Patient



Control tissue (lymph node)

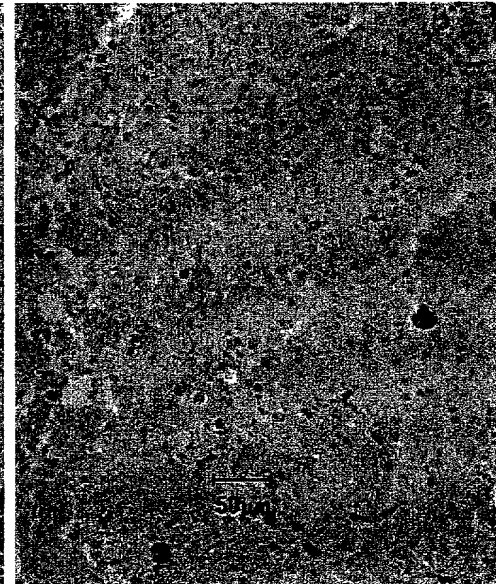


Figure 11



Fig. 12A



Fig 12B

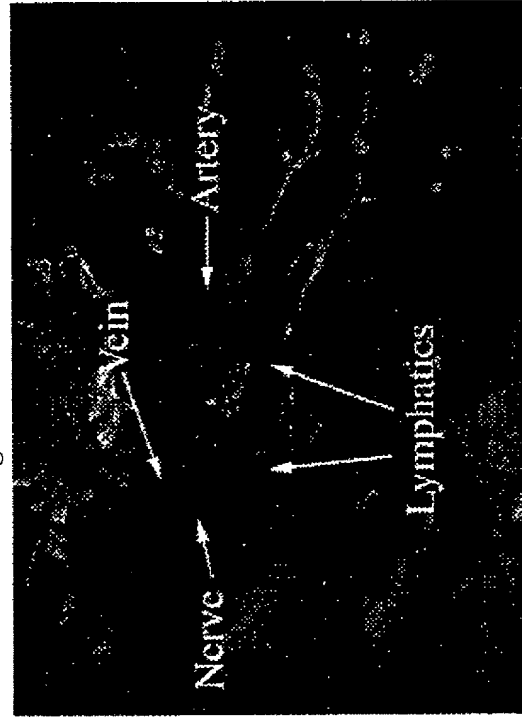
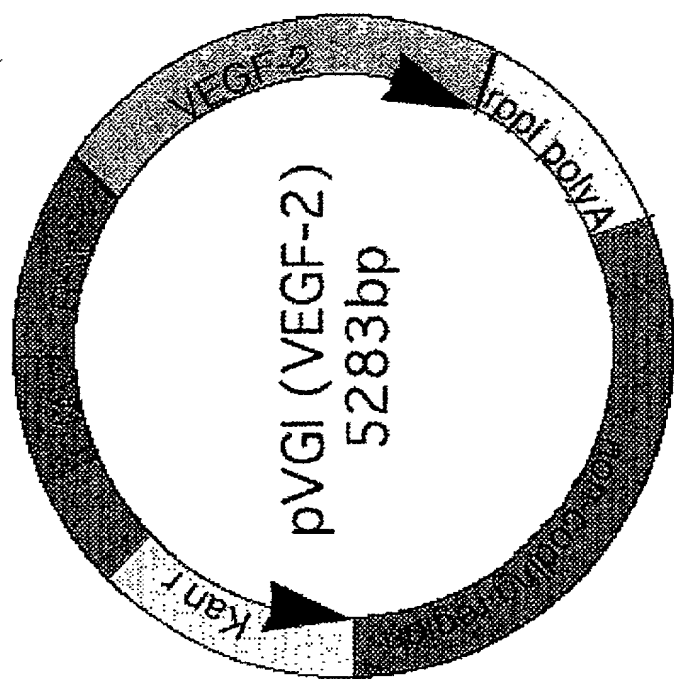


Fig. 12C

A black and white photograph showing a close-up of a dog's head, specifically the ear area. A syringe with a needle is shown inserted into the ear canal. The syringe has a plunger and a graduated scale. The dog's fur is dark and textured. The background is dark and out of focus.



Intradermal and Subcutaneous

500ug



15

6D

D11

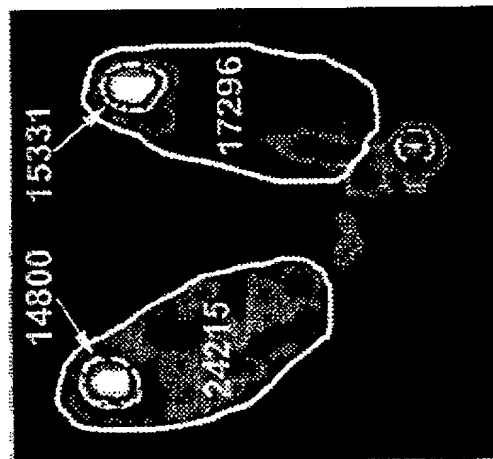
Fig. 13A

Fig. 13B

Page 10 of 10

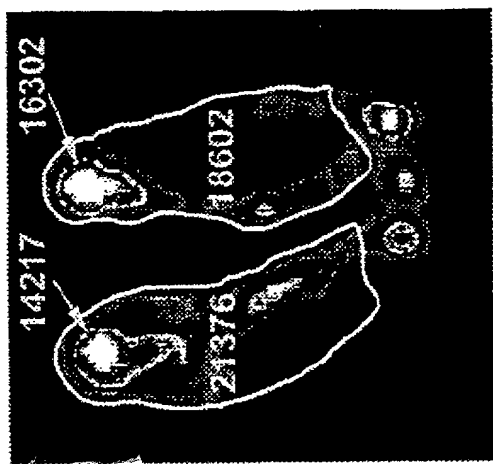


Figs. 14 A-C



$$(24125-14800)/(17296-15331) = 4.75$$

Fig. 15A



$$(21376-14217)/(18602-16302) = 3.11$$

Fig. 15B

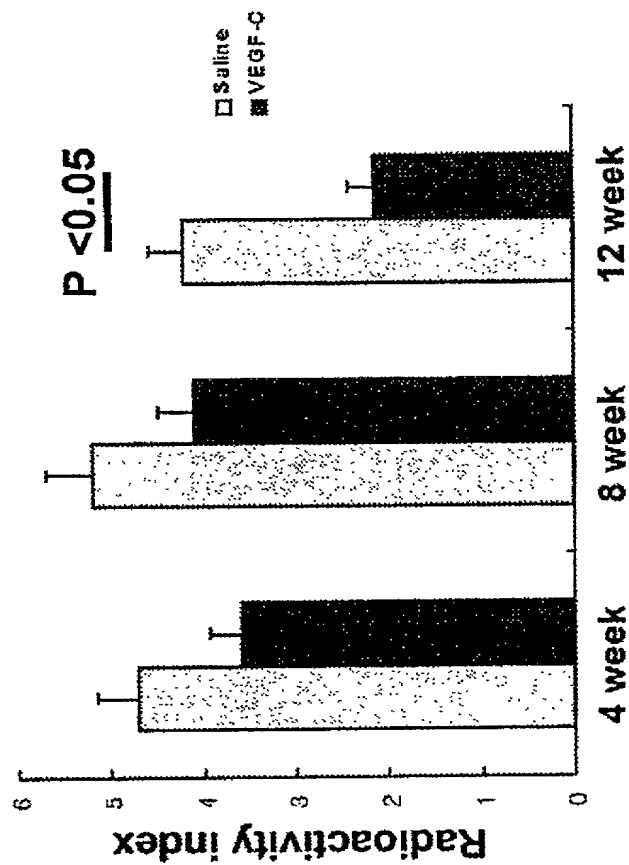
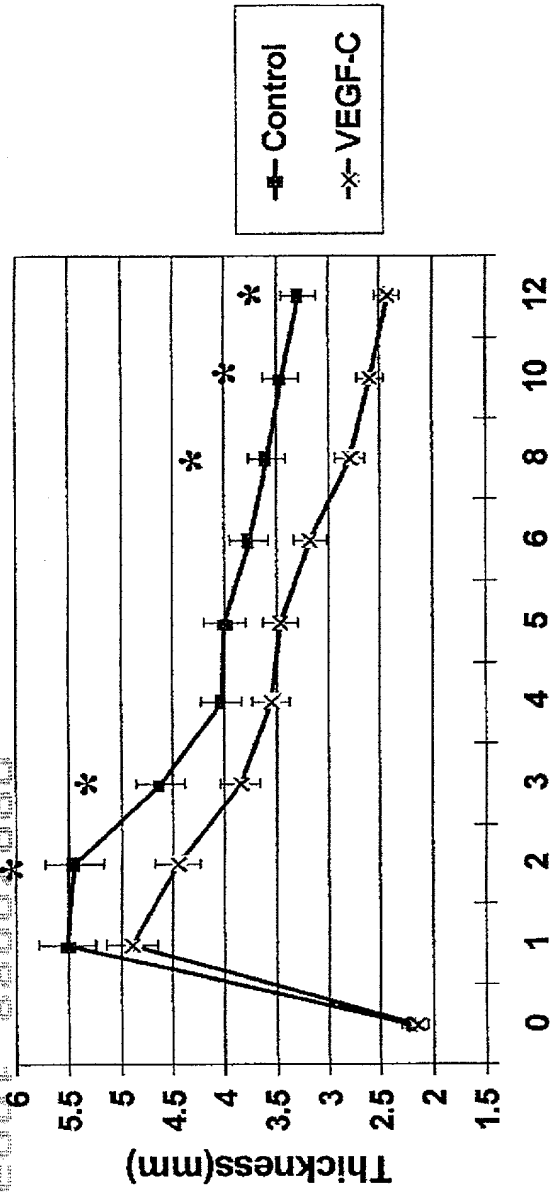


Fig. 15C

Fig. 16A



* P<0.05

Fig. 16A

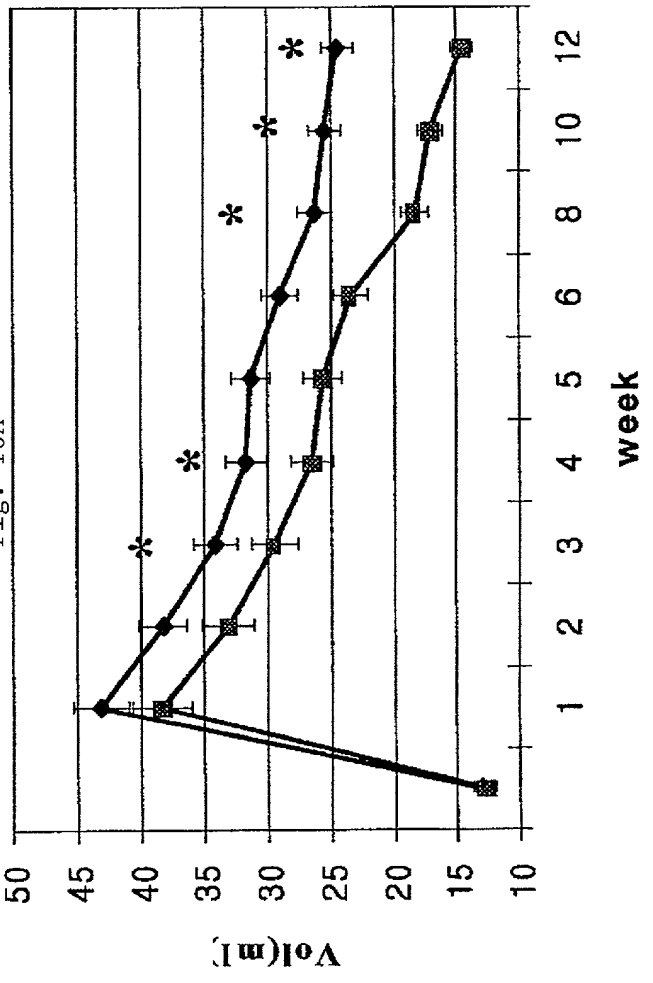
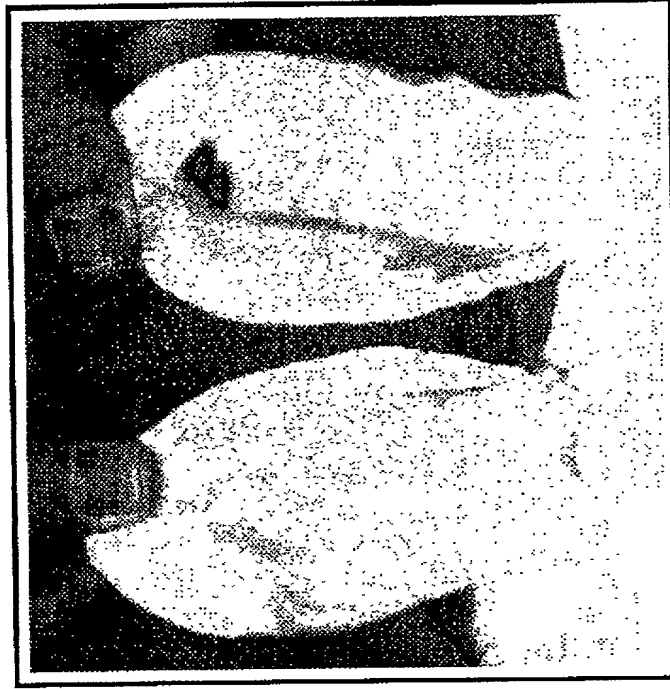
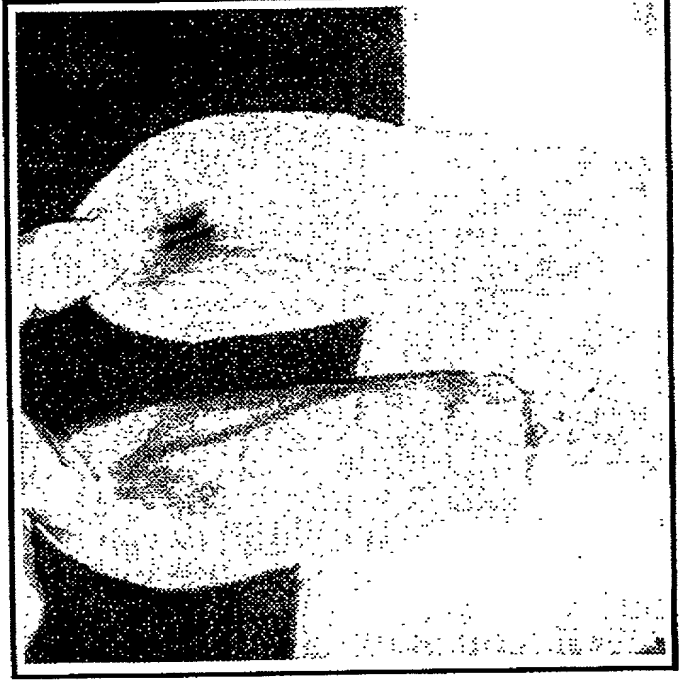


Fig. 16B

Fig. 17 C-D

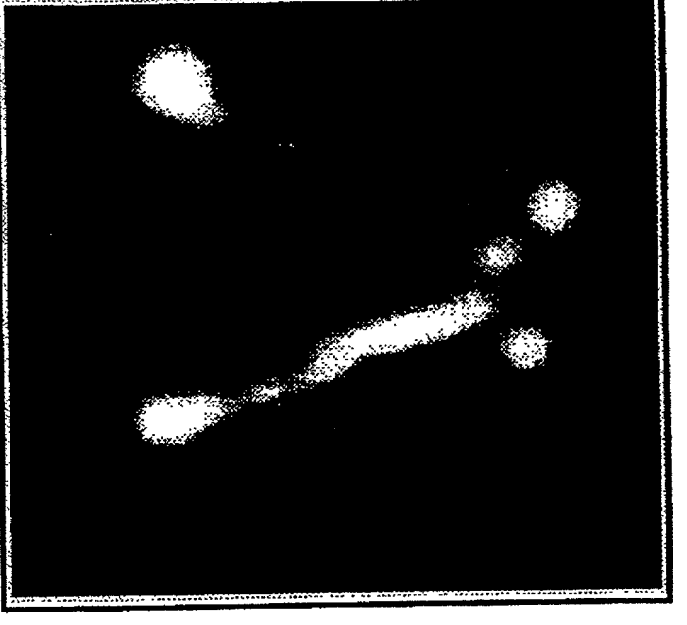


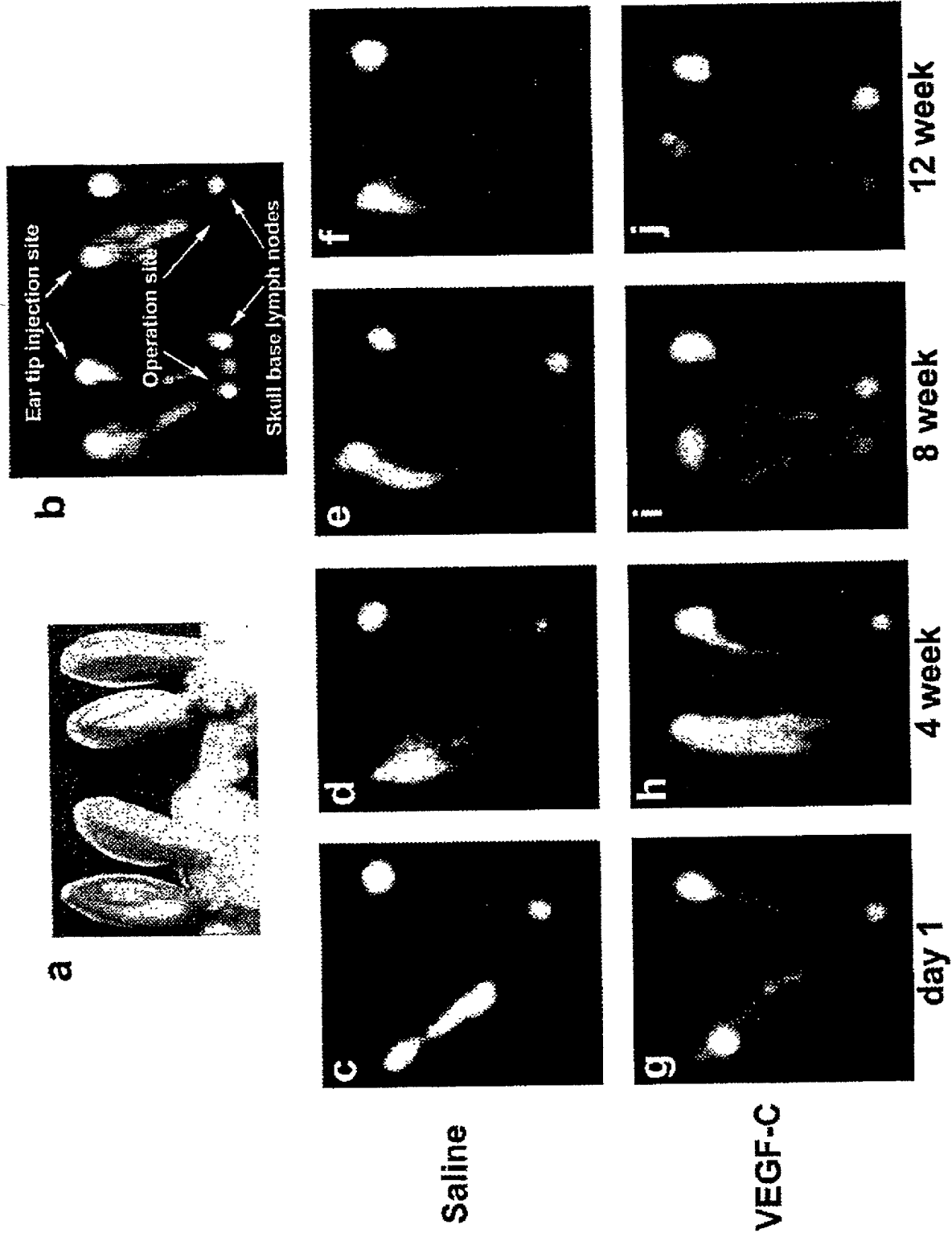
Control



VEGF-C

Fig. 17 C-D





Figs. 19 A-J

VEGF-C

66 kDa —
VEGF-C →



Fig. 20A

α -tubulin

66 kDa —



Prox Mid Dist NL Neg

Fig. 20B

1	rb	CGATGCGGG	TGACCGGGG	ACAGGTGGC	AGCATGGAT	GGTACAAAGA
1	bo	CGGTGGCAG	TGGCTGGAC	GCAGTACCC	AGCATGGAT	GGTACAAAGA
1	hu	CAGTGCTTG	TGGCGGAGC	GCAGCGGCC	AGCATGGAT	GGTACAAAGA
1	no	CGATGCCCG	TGGCTGGAC	GCATGTGCC	AGTATTGAT	GGTACAAAGA
51	rb	TGACAGGCTG	CTGCAAGAG	AATCTGGAT	CGACCTGGG	GACTGGAGC
51	bo	TGAGAAECTG	CTGGAAAGG	AGTCCGGAT	CGACCTGGG	GACTGGAGC
51	hu	CGAGAGGCTG	CTGGAGGAA	AGTCTGGAT	CGACTTGGG	GACTCGAAC
51	no	TGAAAGGCTC	CTGGAGAGG	AGTGGGAAT	CGACCTGGC	GACTCGAATC
101	rb	AGAGGCTGAG	CATCCAGGC	GTGGGGAGG	AGAGGCGGG	CGCTATCTG
101	bo	AGAGGCTGAG	CATCCAGGC	GTGGGGAGG	AGAGGCGGG	CGCTATCTG
101	hu	AGAAAGCTGAG	CATCCAGGC	GTGGGGAGG	AGAGGCGGG	CGCTATCTG
101	no	AGAGGCTGAG	CATCCAGGC	GTGGGGAGG	AGAGGCGGG	CGCTATCTG
151	rb	TGCAAGGCTG	GCAGCGCAA	GGCTGGCTC	AACTCTCGG	CGAGGTAGC
151	bo	TGCAAGGCTG	GCAGCGCAA	GGCTGGCTC	AACTCTCGG	CGAGGTAGC
151	hu	TGCAAGGCTG	GCAGCGCAA	GGCTGGCTC	AACTCTCGG	CGAGGTAGC
151	no	TGCAAGGCTG	GCAGCGCAA	GGCTGGCTC	AACTCTCGG	CGAGGTAGC
201	rb	TGTGGAGGC	GCGAAGATA	AGGCGAGAT	GGAGATGTC	ATCTCTGTC
201	bo	TGTGGAGGC	TCTGAGGATA	AGGCGAGAT	GGAGATGTC	ATCTCTGTC
201	hu	CGTGGAGGC	TGGAGGATA	AGGCGAGAT	GGAGATGTC	ATCTCTGTC
201	no	AGTGGAGGC	TCTGAGGATA	AGGCGAGAT	GGAGATGTC	ATCTCTGTC
251	rb	GCACCGGCT	CATTGGCTG	TTCCTTGGG	TCTCTCTCT	GCTCATCTC
251	bo	GCACCGGCT	CATTGGCTG	TTCCTTGGG	TCTCTCTCT	GCTCATCTC
251	hu	GCACCGGCT	CATTGGCTG	TTCCTTGGG	TCTCTCTCT	GCTCATCTC
251	no	GCACCGGCT	CATTGGCTG	TTCCTTGGG	TCTCTCTCT	GCTCATCTC
301	rb	TGTAAACATGA	GGAGGCCAGC	CCAGCGGAC	ATCAAGACG	GCTACTTGT
301	bo	TGTAAACATGA	GGAGGCCAGC	CCAGCGGAC	ATCAAGACG	GCTACTTGT
301	hu	TGTAAACATGA	GGAGGCCAGC	CCAGCGGAC	ATCAAGACG	GCTACTTGT
301	no	TGTAAACATGA	GGAGGCCAGC	CCAGCGGAC	ATCAAGACG	GCTACTTGT
351	rb	CATCATCATG	GATCCCGGG	AGGTGGCTT	GGAGGAGCA	TGTGAATAC
351	bo	CATCATCATG	GATCCCGGG	AGGTGGCTT	GGAGGAGCA	TGTGAATAC
351	hu	CATCATCATG	GATCCCGGG	AGGTGGCTT	GGAGGAGCA	TGTGAATAC
351	no	CATCATCATG	GATCCCGGG	AGGTGGCTT	GGAGGAGCA	TGTGAATAC
401	rb	TGTCTTACGA	CGCCAGCCAG			
401	bo	TGTCTTACGA	TGTAGTGA			
401	hu	TGTCTTACGA	TGTAGTGA			
401	no	TGTCTTACGA	CGCCAGCCAG			

Fig. 21

rb	1	RCVAGAHVP	SIWYKDERL	LEESGIDLA	DSNQLSLQR	VREEDAGRYL
bo	1	PCPVAGTHVP	SIWYKDEKL	LEESGIDLA	DSNQLSLQR	VREEDAGHYL
hu	1	QCLVAGAHAP	SIWYKDERL	LEESGIDLA	DSNQLSLQR	VREEDAGRYL
mo	1	PCPVAGAHVP	SIWYKDERL	LEESGIDLA	DSNQLSLQR	VREEDAGRYL
rb	51	CSVCNAKGCY	NSSASVAVGG	AEDRGSMEIV	ILVGTGVIAV	FFWVLLLLIF
bo	51	CSVCNAKGCY	NSSASVAVGG	SEDKGSMEIV	ILVGTGVIAV	FFWVLLLLIF
hu	51	CSVCNAKGCY	NSSASVAVGG	SEDKGSMEIV	ILVGTGVIAV	FFWVLLLLIF
mo	51	CSVCNAKGCY	NSSASVAVGG	SEDKGSMEIV	ILVGTGVIAV	FFWVLLLLIF
rb	101	CHNRPPAHAD	KTGYLSIIM	DPGEVPLEEQ	DEVLSYDASQ	
bo	101	CHNRPPAHAD	KTGYLSIIM	DPGEVPLEEQ	DEVLSYDASQ	
hu	101	CHNRPPAHAD	KTGYLSIIM	DPGEVPLEEQ	DEVLSYDASQ	
mo	101	CHNRPPAHAD	KTGYLSIIM	DPGEVPLEEQ	DEVLSYDASQ	

Fig. 22A

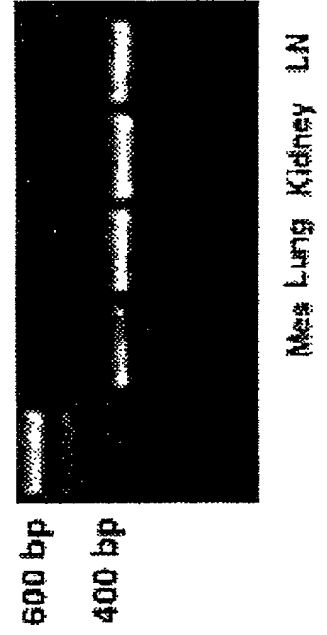


Fig. 22B

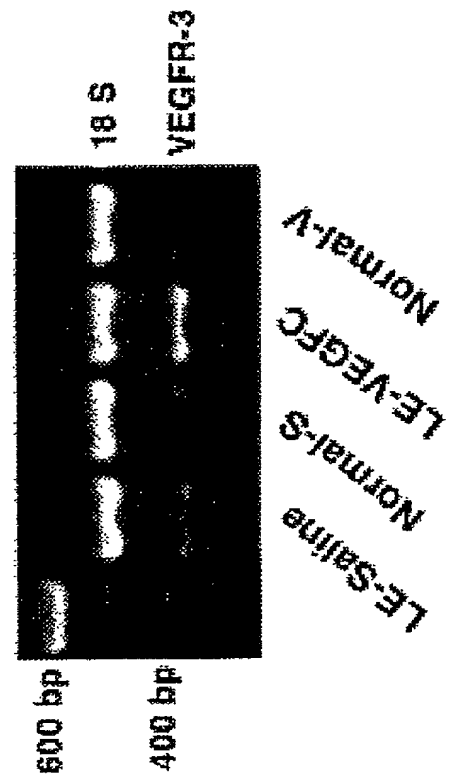


Fig. 22C

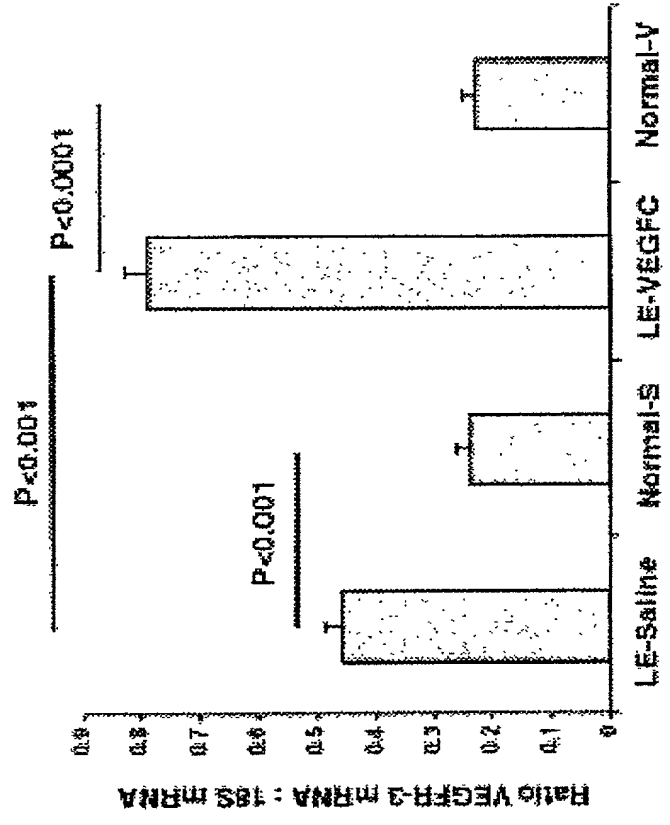


Fig. 22D

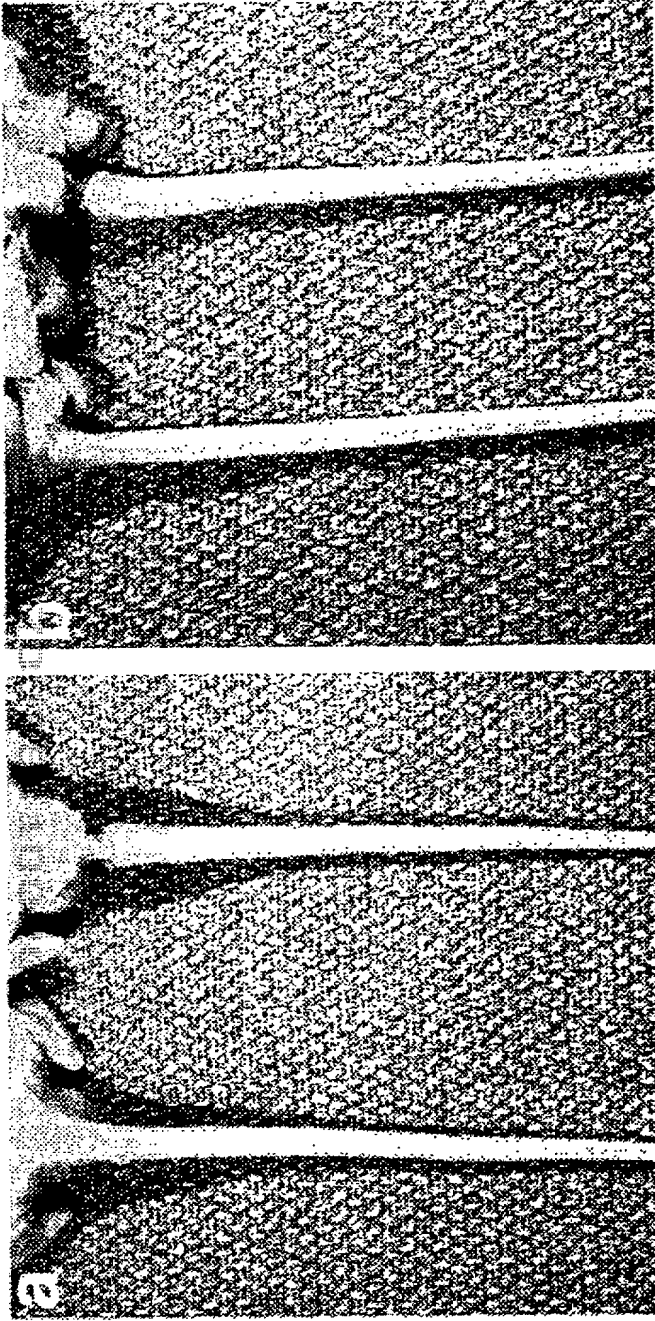


Fig. 23B

Fig. 23A

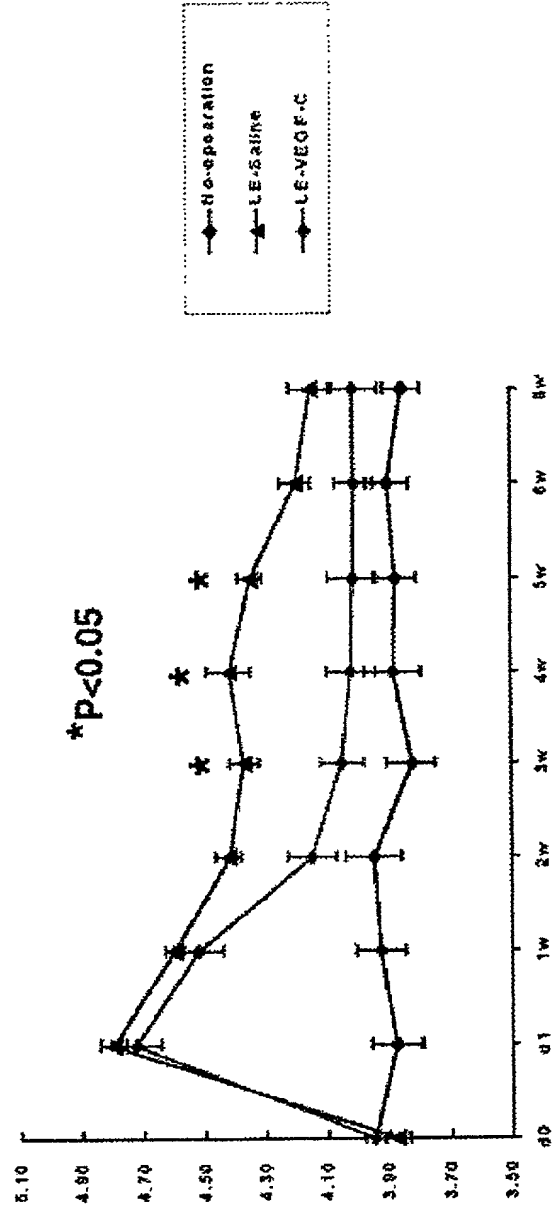


Fig. 23C

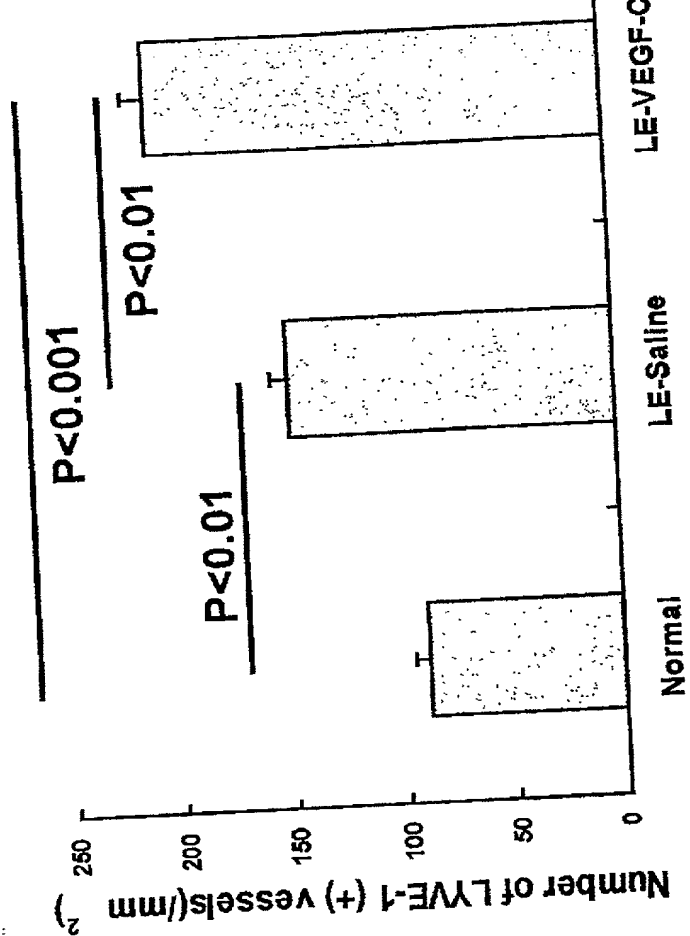
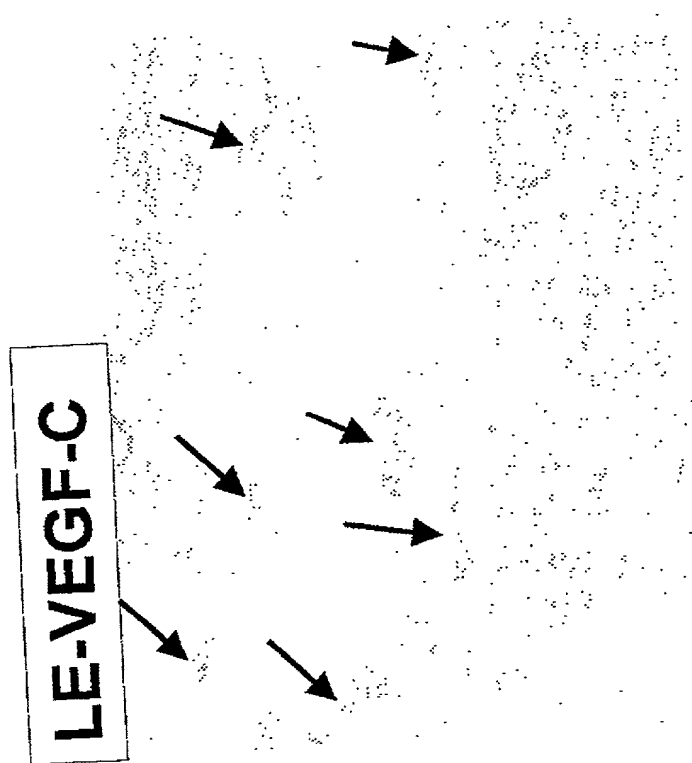
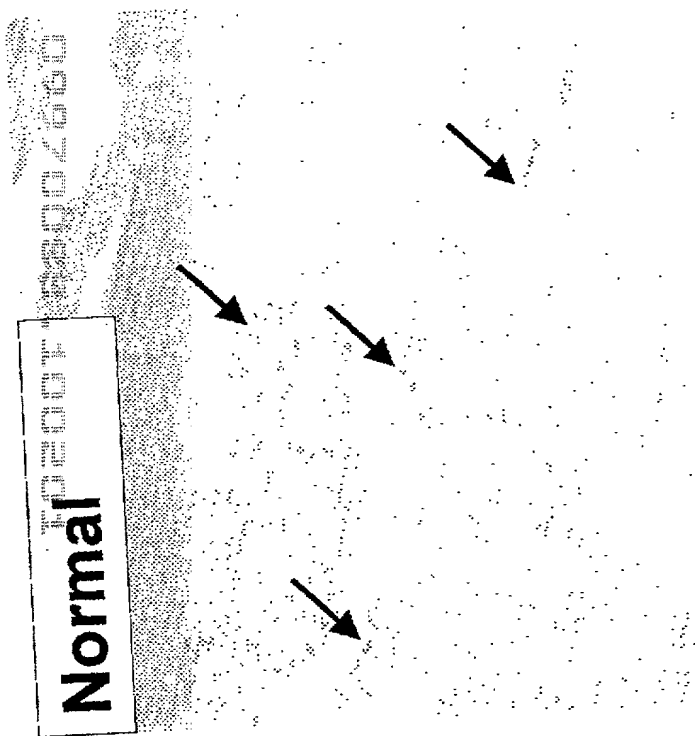
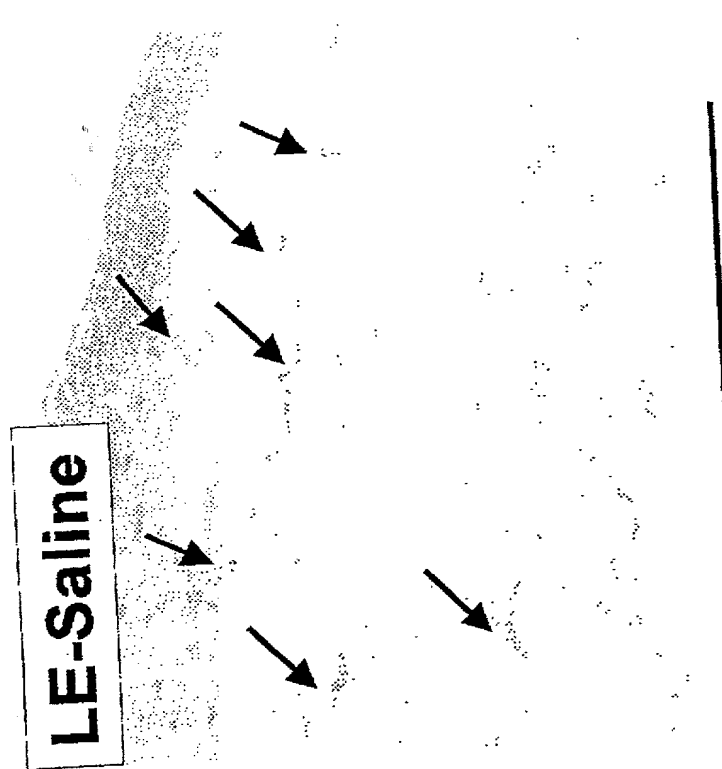


Fig. 24 A-D